REMARKS

The present response is submitted in reply to the Final Office Action issued on January 22, 2008. The Applicants thank the Examiner for the withdrawal of the previous rejections under 35 USC Sections 101 and 112. Claims 3-7 are pending in this application, all of which have been rejected. By the present response, claim 8 has been added which is supported by claim 7 and claims 4 and 5 have been canceled. No new matter has been added. Reconsideration is respectfully requested in light of the following remarks.

Rejection of claims 3-7 under 35 U.S.C. 112, first and/or second paragraphs

Claim 5 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. In particular, the Examiner states that within the structure given in the claim, the "O" at the 14 position of the ring structure does not have a substituent indicating the addition of a group. The Examiner further states that claim 6 further limits claim 5 and the "O" at the 14 position is connected to a group or formula. The Examiner requests that the Applicants complete claim 5 by putting another "R" group to exemplify the invention. The Examiner has interpreted the "O" being at the 14 position being open to contain any group or formula.

Claims 3-7 have been rejected under 35 U.S.C. 112, first paragraph, on the basis that the specification does not reasonably provide enablement for treating diseases mediated by *Helicobacter pylori* and in particular chronic gastritis. The Examiner further states that the specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Applicants respectfully request that the aforementioned rejections be withdrawn, as discussed below.

Regarding the indefinite rejection of claim 5, the Applicants submit that claim 5 recites a pleuromutilin in more detail in that a structural part thereof is unambiguously defined. The Applicants submit that neither a pleuromutilin, nor a structural part thereof, should be considered to be indefinite since one skilled in the art would clearly be aware what a pleuromutilin is. There are numerous discussions of pleuromutilins and pleuromutilin antibiotics on the Internet. For example, reference is made to http://en.wikipedia.org/wiki/Category:Pleuromutilin_antibiotics; http://www.nabriva.com/programs/pleuromutilins; http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1489758, among many others. Therefore, withdrawal of this rejection is requested.

Regarding the rejection of claims 1-7 as being indefinite, at page 5 of the Final Office action, section 2, the Examiner addresses the presence or absence of working examples. The Applicants draw the Examiner's attention to paragraph [0209] of the publication of the present application where the specification confirms that the compounds of the present invention show activity against strains of *H.pylori*, e.g., even against strains of *H.pylori* which are resistant against treatment with known pharmaceuticals and which are known to be useful in the treatment of diseases caused by *H.pylori* infections, e.g., metronidazol resistant strains. Furthermore, the Applicants

respectfully request the Examiner's consideration of the "TABLE TEST" (paragraph [0288]) from which it is evident that compounds of the present invention work in known and acknowledged test systems for determining the activity of *H.pylori* strains, even much better than the known pharmaceuticals against *H.pylori* caused diseases such as metronidazol and tetracycline.

The Applicants note that clearly the effect of pleuromutilins against *H.pylori* activity was unknown at the priority date of the present invention and thus it is not possible that pleuromutilin treatment against *H.pylori* infection could have been mentioned in Malfertheiner, et al. (or Rokkas, et al.), as discussed by the Examiner in the Final Office action. However, the Applicants respectfully submit that in Malfertheiner, et al. and Rokkas, et al. it is clearly taught that a compound which inhibited *H.pylori* activity is appropriate for the treatment of peptic ulcer diseases and gastric adenocarcinoma. That *H.pylori* activity is responsible for peptic ulcer diseases and gastric cancers is also evident from, e.g., Goodman & Gilman's *The Pharmalogical Basis of Therapeutics*, 11th Edition, Section VI, pages 978-979 (copy enclosed). Moreover, it is shown in *Milestones in Drug Therapy*, Macrolide Antibiotics, pages 53, 66 and 71 (copy enclosed) that clarithromycin may be used for *H.pylori* associated gastroduodenal diseases (page 66, first 2 lines) and that clarithromycin has been used for the treatment and prevention of the recurrence of gastroduodenal ulcers caused by *H.pylori* because clarithromycin shows strong antibacterial activity against *H.pylori* (page 66, lines 7-11). Therefore, if a compound shows activity against *H.pylori* it would be evident to one skilled in the art that such compound may be used against diseases which are caused by *H.pylori*.

The Applicants respectfully disagree with the Examiner's position that *in vitro* data is insufficient to show patentability. It is known that for treatment of a disease caused by bacteria, the activity of the corresponding bacteria must be influenced, in the present case inhibited, and that is what the compounds of the present invention do. In particular, they inhibit the activity of the *H.pylori* strains which is thoroughly supported by data. Clinical data can only be provided after long troublesome clinical trials, which may preclude the ability to maintain secrecy of the patent prior to filing.

It is also submitted that one skilled in the art would be immediately aware how to use a compound for the treatment of diseases which are caused by *H.pylori*, namely, according to the experience with other compounds which are active against *H.pylori* via analogous handling.

It is again noted that the presently claimed invention has been deemed patentable in the corresponding European application. Although it is appreciated that the Examiner is not obligated to consider the patentability from a foreign patent office, the Applicants wish to bring this to the Examiner's attention.

In view of the above arguments and amendments, withdrawal of the rejections and objections is respectfully requested.

Conclusion

In light of the foregoing claims and arguments, it is believed that the present application is in condition for allowance, and such action is earnestly solicited. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

Date: July 8, 2009

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Gilman's

The Pharmacological Basis of THERAPEUTICS

eleventh edition

L. Brunton
ith L. Parker

twice-daily dosing with a proton pump inhibitor may be needed. However, it is difficult if not impossible to render patients achlorhydric—even on twice-daily doses of proton pump inhibitors—and two-thirds or more of subjects will continue to make acid, particularly at night. This phenomenon, called *nocturnal acid breakthrough*, has been invoked as a cause of refractory symptoms in some patients with GERD. However, decreases in gastric pH at night while on therapy generally are not associated with acid reflux into the esophagus, and the rationale for suppressing nocturnal acid secretion (even if feasible) remains to be established. Nevertheless, patients with continuing symptoms on twice-daily proton pump inhibitors are often treated by adding an H_2 receptor antagonist at night. While this can further suppress acid production, the effect is short-lived, probably due to the development of tolerance, as described above (Fackler *et al.*, 2002).

Therapy for Extraintestinal Manifestations of GERD. With varying levels of evidence, acid reflux has been implicated in a variety of atypical symptoms, including noncardiac chest pain, asthma, laryngitis, chronic cough, and other ear, nose, and throat conditions. Proton pump inhibitors have been used with some success in certain patients with these disorders, generally in higher doses and for longer periods of time than those used for patients with more classic symptoms of GERD.

GERD and Pregnancy. Heartburn is estimated to occur in 30% to 50% of pregnancies, with an incidence approaching 80% in some populations (Richter, 2003). In the vast majority of cases, GERD ends soon after delivery and thus does not represent an exacerbation of a preexisting condition. Nevertheless, because of its high prevalence and the fact that it can contribute to the nausea of pregnancy, treatment often is required. Treatment choice in this setting is complicated by the paucity of data for the most commonly used drugs. In general, most drugs used to treat GERD fall in FDA Category B, with the exception of omeprazole (FDA Category C).

Mild cases of GERD during pregnancy should be treated conservatively; antacids or sucralfate are considered the first-line drugs. If symptoms persist, H_2 receptor antagonists can be used, with ranitidine having the most established track record in this setting. Proton pump inhibitors are reserved for women with intractable symptoms or complicated reflux disease. In these situations, lansoprazole is considered the preferred choice among the proton pump inhibitors, based on animal data and available experience in pregnant women.

Peptic Ulcer Disease

The pathophysiology of peptic ulcer disease is best viewed as an imbalance between mucosal defense factors (bicarbonate, mucin, prostaglandin, nitric oxide, and other peptides and growth factors) and injurious factors (acid and pepsin). On average, patients with duodenal ulcers produce more acid than do control subjects, particularly at night (basal secretion). Although patients with gastric ulcers have normal or even diminished acid production, ulcers rarely if ever occur in the complete absence of acid. Presumably, a weakened mucosal defense and reduced bicarbonate production contribute to the injury from the relative
of acid in these patients. *H. pylori* and exo
such as nonsteroidal antiinflammatory dru
interact in complex ways to cause an ulce
of peptic ulcers are associated with *H. py*
of the stomach. This infection may lead to
duction of somatostatin by D cells, and in ti
inhibition of gastrin production; resulting
acid production and reduced duodenal
production.

NSAIDs also are very frequently associa
tic ulcers (in up to 60% of patients, parti
with complications such as bleeding). Topi
the luminal presence of the drug appears to
role in the pathogenesis of these ulcers, as
the fact that ulcers can occur with very low d
rin (10 mg) or with parenteral administration
The effects of these drugs are instead media
cally; the critical element is suppression of
tive form of cyclooxygenase-1 (COX-1) in
and decreased production of the cytoprote
glandins PGE_2 and PGI_2.

Table 36–4 summarizes current recomme
drug therapy of gastroduodenal ulcers. P
inhibitors relieve symptoms of duodenal ulc
mote healing more rapidly than do H_2 rece
nists, although both classes of drugs are ve
in this setting. Peptic ulcer represents a chro
and recurrence within 1 year is expected in
of patients who do not receive prophylac
pression. With the appreciation that *H. py*
major etiopathogenic role in the majorit
ulcers (*see* below), prevention of relapse is
eliminating this organism from the stoma
acid suppression, once the mainstay of ulcer
now is used mainly in patients who are *H. p*
tive or, in some cases, for maximum pr
recurrence in patients who have had life
complications.

Intravenous pantoprazole or lansoprazole
preferred therapy in patients with acute bleed
The theoretical benefit of maximal acid sup
this setting is to accelerate healing of the under
In addition, a higher gastric pH enhances clo
and retards clot dissolution.

Treatment of Helicobacter pylori *Infection.* *H. pylori*, a gram-negative rod, has been associated w
and the subsequent development of gastric ap
ulcers, gastric adenocarcinoma, and gastric
phoma (Suerbaum and Michetti, 2002). Be

...Treatment of Gastroduodenal Ulcers

	ACTIVE ULCER	MAINTENANCE THERAPY
...onists		
	800 mg at bedtime/400 mg twice daily	400 mg at bedtime
	40 mg at bedtime	20 mg at bedtime
...idine	300 mg after evening meal or at bedtime/150 mg twice daily	150 mg at bedtime
...hibitors		
	15 mg (DU; NSAID risk reduction) daily	
	30 mg (GU including NSAID-associated) daily	
	20 mg daily	
	20 mg daily	
...alogs		
	200 μg four times daily (NSAID-associated ulcer prevention)*	

...gastric ulcer. *Only misoprostol 800 μg/day has been directly shown to reduce the risk of ulcer complications such as perforation or obstruction (Rostom *et al*, 2004).

...*H. pylori* in the pathogenesis of peptic ... this infection is standard care in ... or duodenal ulcers. Provided that ...ing NSAIDs, this strategy almost com... the risk of ulcer recurrence. Eradication ... indicated in the treatment of mucosa-associated tissue lymphomas of the stomach; ... significantly after such treatment.

...ers for *H. pylori* eradication have been ...nce-based literature review suggests that ...men in this setting should achieve a cure ...80%. Five important considerations influ... of an eradication regimen (Graham, ...6-5). First, single-antibiotic regimens are ...dicating *H. pylori* infection and lead to ...stance. Combination therapy with two or ... (plus acid-suppressive therapy) is asso... highest rate of *H. pylori* eradication. Sec... pump inhibitor or H_2 receptor antagonist ...nhances the effectiveness of *H. pylori* ...mens containing *amoxicillin* or *clarithro*... regimen of 10 to 14 days of treatment ...better than shorter treatment regimens; in ...ries, a 14-day course of therapy generally ...fourth, poor patient compliance is linked to ...-related side effects experienced by as ...of patients taking triple-agent regimens, ...nvenience of three- or four-drug regimens ...several times per day. Packaging that com... doses into one convenient unit is available and may improve patient compliance (Table 36–5). Finally, the emergence of resistance to clarithromycin and *metronidazole* increasingly is recognized as an important factor in the failure to eradicate *H. pylori*. Clarithromycin resistance is related to mutations that prevent binding of the antibiotic to the ribosomes of the pathogen and is an all-or-none phenomenon. In contrast, metronidazole resistance is relative rather than absolute and may involve several adaptations by the bacteria. In the presence of *in vitro* evidence of resistance to metronidazole, amoxicillin should be used instead. In areas with a high frequency of resistance to clarithromycin and metronidazole, a 14-day, quadruple-drug regimen (three antibiotics combined with a proton pump inhibitor) generally is effective therapy.

NSAID-Related Ulcers. Chronic NSAID users have a 2% to 4% risk of developing a symptomatic ulcer, gastrointestinal bleeding, or perforation. Ideally, NSAIDs should be discontinued in patients with an ulcer if at all possible. If continued therapy is needed, selective COX-2 inhibitors may be considered, although this does not eliminate the risk of subsequent ulcer formation and the possible association of these drugs with adverse cardiovascular events mandates caution (*see* Chapter 25). Healing of ulcers despite continued NSAID use is possible with the use of acid-suppressant agents, usually at higher doses and for a considerably longer duration than standard regimens (*e.g.*, 8 weeks or longer). Again, proton pump inhibitors are superior to H_2 receptor antagonists and misoprostol in promoting the healing of active ulcers (healing rates of 80% to 90% for proton pump inhibitors *versus* 60% to 75% for the H_2 receptor antagonists), and in preventing recurrence of gastric and duodenal ulcers in the setting of continued NSAID administration (Lanza, 1998).

Table 36–5
Therapy of Helicobacter pylori *Infection*

Triple therapy × 14 days: [Proton pump inhibitor + clarithromycin 500 mg + (metronidazole 500 mg or amoxicillin 1 g)] twice a day. (Tetracycline 500 mg can be substituted for amoxicillin or metronidazole.)
Quadruple therapy × 14 days: Proton pump inhibitor twice a day + metronidazole 500 mg three times daily + (bismuth subsalicylate 525 mg + tetracycline 500 mg four times daily)
or
H_2 receptor antagonist twice a day + (bismuth subsalicylate 525 mg + metronidazole 250 mg + tetracycline 500 mg) four times daily
Dosages:

Proton pump inhibitors:	H_2 receptor antagonists:
Omeprazole: 20 mg	Cimetidine: 400 mg
Lansoprazole: 30 mg	Famotidine: 20 mg
Rabeprazole: 20 mg	Nizatidine: 150 mg
Pantoprazole: 40 mg	Ranitidine: 150 mg
Esomeprazole: 40 mg	

See Howden and Hunt, 1998.

Stress-Related Ulcers. Stress ulcers are ulcers of the stomach or duodenum that occur in the context of a profound illness or trauma requiring intensive care. The etiology of stress-related ulcers differs somewhat from that of other peptic ulcers, involving acid and mucosal ischemia. Because of limitations on the oral administration of drugs in many patients with stress-related ulcers, intravenous H_2 receptor antagonists have been used extensively to reduce the incidence of GI hemorrhage due to stress ulcers. Now that intravenous preparations of proton pump inhibitors are available, it is likely that they will prove to be equally beneficial. *However, there is some concern over the risk of pneumonia secondary to gastric colonization by bacteria in an alkaline milieu.* In this setting, sucralfate appears to provide reasonable prophylaxis against bleeding without increasing the risk of aspiration pneumonia. This approach also appears to provide reasonable prophylaxis against bleeding, but is less convenient (Cook *et al.*, 1998).

Zollinger-Ellison Syndrome. Patients with this syndrome develop pancreatic or duodenal gastrinomas that stimulate the secretion of very large amounts of acid, sometimes in the setting of multiple endocrine neoplasia, type I. This can lead to severe gastroduodenal ulceration and other consequences of uncontrolled hyperchlorhydria. Proton pump inhibitors clearly are the drugs of choice, usually given at twice the routine dosage for peptic ulcers with the therapeutic goal of reducing acid secretion to 1 to 10 mmol/h.

Nonulcer Dyspepsia. This term refers to ulcer-like symptoms in patients who lack overt gastroduodenal ulceration. It may be associated with gastritis (with or without *H. pylori*) or with NSAID use, but the pathogenesis of this syndrome remains controversial.

Although empirical treatment with acid-suppr
routinely in patients with nonulcer dyspepsia, t
evidence of their benefit in controlled trials.

CLINICAL SUMMARY

The control of acid-peptic disease repres
umph for modern pharmacology. Proton pu
considered superior for acid suppression i
significant acid-peptic diseases, including
reflux disease, peptic ulcers, and NSAID
Proton pump inhibitors also are employed
with antibiotics to eradicate infection with
thereby play a role in preventing recurren
These agents largely have replaced the use
and sucralfate, although the latter still is a lo
tive for prophylaxis against stress ulcers. The
mal inhibition of acid secretion with the proto
tors (3 to 5 days) makes them less suited
as-needed basis for symptom relief. In this se
tor antagonists, while less effective than prote
itors in suppressing acid secretion, have a mo
of action that makes them useful for patien
agement of mild or infrequent symptoms.

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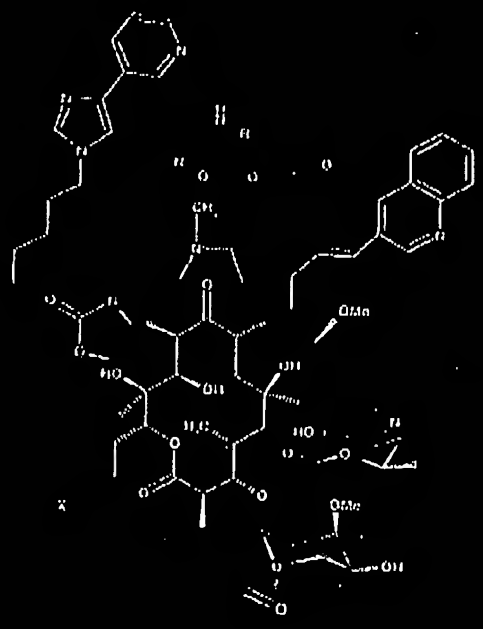

Birkhäuser

Clarithromycin and new derivatives of erythromycin

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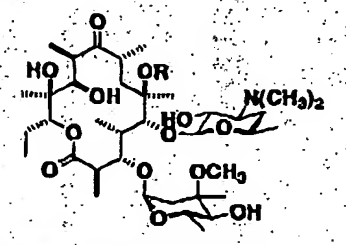
Introduction

Since erythromycin's the discovery in 1952 [1], it has been one of the most useful macrolide antibiotics, having the highest antibacterial activity and low toxicity. In order to achieve high antibacterial activities against a wide variety of pathogens and favorable pharmacokinetic properties, tremendous efforts have been made related to chemical modification [2, 3]. In the 1970s and 1980s, dirithromycin, flurithromycin, and davercin were synthesized and evaluated. Erythromycin itself is quite unstable under acidic conditions, so esters, salts, and various formulations also have been developed.

At Taisho Pharmaceutical Co. Ltd., we were interested in the role of the hydroxyl groups of erythromycin (2), and a series of *O*-alkylated derivatives was synthesized [4–8]. Among them, clarithromycin (6-*O*-methylerythromycin A, 1) exhibited antibacterial activities against aerobic gram-positive bacteria, some gram-negative bacteria, anaerobic bacteria, *Mycoplasma*, and *Chlamydia*. The antibacterial activities of clarithromycin were equal to or two-fold better than erythromycin A (2) *in vitro*. However, clarithromycin is fairly stable in acidic conditions due to 6-*O*-methylation, which brought about excellent biological properties, especially *in vivo* antibacterial activities, pharmacokinetic properties, and metabolism. The structural difference between clarithromycin and erythromycin is only the 6-*O*-methyl group, but the biological properties of clarithromycin were improved considerably.



Clarithromycin (1) R=CH_3
Erythromycin A (2) R=H

Figure 1. Structures of clarithromycin (1) and erythromycin A (2).

Additional clinical applications of clarithromycin for the treatment of mycobacterial infections and *Helicobacter pylori*-associated gastroduodenal disease have been approved. Disseminated *Mycobacterium avium* complex (MAC) infection is a common opportunistic disease in AIDS patients and is associated with significant morbidity and mortality. Clarithromycin, having strong antibacterial activities against this pathogen, is useful for the treatment and prevention of MAC infections [45–47]. Clarithromycin has been used for treatment and prevention of the recurrence of gastroduodenal ulcers caused by *H. pylori* by combination therapy with β-lactam antibiotics and proton pump inhibitors. The strong antibacterial activity of clarithromycin against *H. pylori* and high acid stability are thought to contribute to the efficacy [48–51].

Long-term administration of erythromycin as well as clarithromycin is useful for the treatment of diffuse panbronchiolitis (DPB). DPB is a disease characterized by chronic inflammation of the respiratory bronchioles and the infiltration of chronic inflammatory cells. The disease results in respiratory failure due to infection by *Pseudomonas aeruginosa* or *H. influenzae* and was previously difficult to treat. The efficacy of erythromycin for this disease was reported in 1987 [52]. Erythromycin and clarithromycin do not show antibacterial activity against *P. aeruginosa*, but they do improve pulmonary functions [53]. Efficacy of 16-membered macrolides has not been reported.

The mechanism of 14-membered macrolides in DPB has been investigated, and new biological properties of macrolides have been revealed. For example, erythromycin inhibited respiratory glycoconjugate secretion [54] and chloride secretion across canine tracheal cells [55]. The number of neutrophils and the neutrophil-derived elastolytic-like activity in bronchoalveolar lavage fluid decreased after treatment with erythromycin along with a significant improvement in pulmonary function [56]. Erythromycin inhibited intrapulmonary influx of neutrophils in mice with intratrachial injection of recombinant IL-8 [57]. Erythromycin suppressed the proliferation of lymphocytes [58] and promoted differentiation of monocytes to macrophages [59]. Many pathogens produce glycocalyx and form biofilm. Erythromycin and clarithromycin degraded the biofilm, which may be related to the efficacy in the treatment of DPB [60].

Recent chemical modification of erythromycin

In the early 1990s, three new macrolides, clarithromycin, roxithromycin, and azithromycin, were developed, and they have expanded the indications of this class of drug into new therapeutic areas. For further improvement of erythromycin derivatives, macrolide resistant *S. pneumoniae* and *H. influenzae* have been regarded as key pathogens.

At Taisho Pharmaceutical Co., Ltd., chemical modification has been continued and a new class of macrolides has been synthesized (Fig. 4).

TE-802 (32), a 9,11,12-tricyclic ketolide, exhibited strong *in vitro* antibacterial activities against both erythromycin-susceptible bacteria and erythromycin-resis-

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Sent: Thursday, June 25, 2009 10:27 AM

To: 'office@kopas.at'

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